REMARKS

I. Status of the claims

Claims 1-34, 36-69, 71-142, 144-151, 153-168 stand rejected. Claims 1, 10, 11, 68, 71, 72, 74, 84, 85, 106, 109, 141, 144, and 145 have been amended, and claims 8, 9, 12, 81, 86, and 108 have been canceled. Claims 1-7, 10, 11, 13,-34, 36-69, 71-80, 82-85, 87-107, 109-142, 144-151 and 153-168 are pending in the application upon entry of these amendments.

II. Amendments to the claims

Claims 1 and 74 have been amended to replace the term "water-miscible organic solvent" with the term "C1-C3 alcohol." Support for this amendment can be found, for example, at page 24 of the specification and claim 82 as filed. Claims 1 and 74 also have been amended to recite that the liposome has a mean diameter of less than 400 nm. Support for this amendment can be found at page 18 of the specification. Claims 10, 11, 84, 85, and 109 have been amended to correct their dependencies or to amend certain claim terms in light of the amendments to claims 1 and 74 and the cancellation of claims 8, 9, 12, 81, 86 and 108. Claims 1, 74, 68, 71, 72, 106, 141, 144 and 145 have been amended for clarity by removing the reference to step (A). No new matter has been added.

III. Rejections under 35 U.S.C. § 103

A. Papahadjopolous in view of Kikuchi and Meers

The Examiner has rejected claims 1-16, 25, 29-31, 33, 34, 36-69, 71-81, 87-90, 99, 102-104, 106-142, 144-147 and 153-168 as being unpatentable over U.S. Patent No. 4,235,871 to Papahadjopolous et al. ("Papahadjopolous") in view of U.S. Patent No. 4,687,661 to Kikuchi et al.

("Kikuchi") and U.S. Patent No. 4,235,871 to Meers et al. ("Meers"). The Examiner contends that it would have been obvious to one of skill in the art at the time of the invention to combine the water miscible solvent of Kikuchi and to use the lipid of Meers (i.e., N-acylphosphatidylethanolamines) with the teachings of Papahadjopolous. *Office action* at p. 2-3. Applicants respectfully traverse.

In order to establish a *prima facie* case of obviousness, the Examiner must determine the scope and content of the prior art, ascertain the differences between the claimed invention and the prior art and resolve the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1, 148 (1966). Once the Graham factual inquiries have been resolved, the Examiner must explain why the differences between the cited references and the claims would have been obvious to one of ordinary skill in the art. Fed. Reg. Vol. 72, No. 195, p. 57527. The Supreme Court in *KSR* stressed that "obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR* 127 S.Ct. 1727, 1740 (2007); see also Fed. Reg. Vol. 72, No. 195, p. 57529. "The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. Fed. Reg. Vol. 72, No. 195 at p. 57528.

Applicants respectfully submit that the cited documents do not render the amended claims obvious because there is no rational basis for a person skilled in the are to modify the references, as the Examiner suggests, with any reasonable expectation of success. Specifically, the claims as amended recite that the gel comprises a C_1-C_3 alcohol. Papahadjopolous describes a method of encapsulating biologically active materials in lipid vesicles. In particular, the method of Papahadjopolous ***requires*** the use of a ***water-immiscible*** organic solvent for forming "inverted

micelles". *Papahadjopolous* at col. 3, ll. 48-50. An aqueous mixture containing the biologically active material for encapsulation is added to the water-immiscible organic phase to produce a 2-phase mixture that is then emulsified. It is only when the organic phase is removed from the aqueous phase that the "inverted micelles" revert to a bilayer–like structure to form large oligolamellar vesicles containing large amounts of aqueous phase. *Id.* at col. 3, ll. 50-53. Papahadjopolous emphasizes that emulsification and removal of the organic phase prior to final dissolution in an aqueous phase is "essential for high capture percentage in this method and is a critical difference between the process of our invention and all previous methods described." *Id.* at col. 6, ll. 56-61. Based on these teachings, the skilled artisan would have no reasonable expectation of success in using a C_1-C_3 alcohol instead of a water immiscible organic solvent.

Kikuchi and Meers fail to overcome the deficiencies of Papahadjopolous. Kikuchi teaches that "[w]hen the drug is water-soluble and miscible with a water-soluble organic solvent . . . it is more efficient to mix it with the water-soluble organic solvent . . . ." *Kikuchi* at col. 4. ll. 3-8. Those of ordinary skill in the art know that nucleic acids are not soluble in C_1-C_3 alcohols, and would expect that the addition of a C_1-C_3 alcohol would cause the nucleic acid to come out of solution. For example, in the attached pages from Volumes 2 and 3 of "Molecular Cloning: A Laboratory Manual," demonstrate the precipitation of nucleic acids using ethanol and isopropanol. Thus, Kikuchi also teaches against using a C_1-C_3 alcohol to encapsulate a nucleic acid in a liposome. Meers is relied on merely for described n-acyl phosphatidylethanolamines, and does not provide support for the use of a C_1-C_3 alcohol, as claimed.

Moreover, Kikuchi further emphasizes the use of non-volatile organic solvents, such as glycerols, which remain in the formulation, in contrast to the volatile C_1-C_3 alcohols of the present claims.

Applicants further respectfully remind the Examiner that a reference must be considered in its entirety, for all that it teaches, including disclosures that teach away from the claimed invention. M.P.E.P. § 2142.02. Under *KSR*, "teaching away" still provides evidence of non-obviousness. *See* 127 S.Ct. at 1745. "[P]roceeding contrary to accepted wisdom in the art is evidence of nonobviousness." M.P.E.P. §2145 (citing *in re Hedges*, 783 F.2d 1083 (Fed. Cir. 1986)). Papahadjopolous makes it clear that emulsification and removal of the water-immiscible organic solvent are required for encapsulation. Kikuchi stresses the importance of solubilizing the bioactive agent to be encapsulated in the liposome. Thus, the skilled artisan, upon reading Papahadjopolous in view of Kikuchi would be led away from the use of a C_1-C_3 alcohol as claimed because C_1-C_3 alcohols are water miscible and would fail to solubilize the nucleic acid.

For at least these reasons, Applicants respectfully submit that Papahadjopolous in view of Kikuchi and Meers fails to render the presently claimed methods obvious. Withdrawal of this rejection is respectfully requested.

B. Papahadjopolous in view of Kikuchi, Meers and Eppstein

The Examiner has rejected claims 17-24, 26-28, 32, 91-98, 100, 101, 105 and 148-151 as being unpatentable over Papahadjopolous, Kikuchi and Meers, as applied to claims 1-16, 25, 29-31, 33, 34, 36-69, 71-81, 87-90, 99, 102-104, 106-142, 144-147 and 153-168 above, and further in view of U.S. Patent No. 4,897,355 to Eppstein et al. ("Eppstein") taken with evidence of GenBank Accession No. M77788. The Examiner relies on Eppstein for teaching that liposomes could be used

to encapsulate and deliver plasmid DNA or oligonucleotides; the use of the lipids such as DOPC and DPPC; methods of transfecting eukaryotic cells in vitro at 37 °C; and intravenous delivery to humans. *Office Action* at p. 6. Applicants respectfully traverse.

As discussed above, Papahadjopolous in view of Kikuchi and Meers teaches against the use of a C_1-C_3 alcohol. Nothing in Eppstein overcomes the deficiencies of these teachings described above. Therefore, Papahadjopolous in view of Eppstein, Kikuchi and Meers fails to render the presently claimed methods obvious. Accordingly, withdrawal of this rejection is respectfully requested.

C. Papahadjopolous in view of Kikuchi, Meers and Lenk

The Examiner has rejected claims 82-86 as being unpatentable over Papahadjopolous, Kikuchi and Meers, as applied to claims 1-16, 25, 29-31, 33, 34, 36-69, 71-81, 87-90, 99, 102-104, 106-142, 144-147 and 153-168 above, and further in view of U.S. Patent No. 5,169,637 to Lenk et al. ("Lenk"). The Examiner states that Papahadjopolous, Kikuchi and Meers do not specifically teach acetone, ethanol, methanol, or 2-propanol as water-miscible organic solvents. The Examiner relies on Lenk to disclose the aforementioned solvents and contends " [i]t would have been obvious to use acetone, ethanol, methanol, or 2-propanol because Lenk taught that these can be used to solubilize lipids. *Office Action* at page 8. Applicants respectfully traverse.

As discussed above, Papahadjopolous in view of Kikuchi and Meers teaches against the use of a C_1 to C_3 alcohol, for example methanol, ethanol and 2-propanol as taught in Lenk. For the same reasons discussed above, the skilled artisan would expect a nucleic acid to come out of solution in the presence of a C_1 to C_3 alcohol. Moreover, Lenk requires evaporation of the water/solvent mixture to form the liposome. *Lenk* at col. 9, ll. 45-55. The present claims, in

contrast, provide a method of "directly" forming the liposomes, without an evaporation step. For at least these reasons, withdrawal of this rejection is respectfully requested.

IV. Conclusion

In light of the amendments and remarks set forth above, Applicants submit that the pending claims are in condition for allowance. Reconsideration and timely allowance of the pending claims is respectfully solicited. If a telephone conference would be helpful, the Examiner is invited to call the undersigned at 617-832-1223. Applicants hereby request that any additional fees required for timely consideration of this application be charged to **Deposit Account No. 06-1448, Reference TRA-027.01.**

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